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Genetic polymorphisms of Th2 interleukins, history of asthma or eczema and childhood acute lymphoid leukaemia: Findings from the ESCALE study (SFCE)

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ABSTRACT

Background: Previous studies on the putative role of allergy in the aetiology of childhood leukaemia have reported contradictory results. The present study aimed to analyse the relation between a medical history of asthma or eczema and childhood acute lymphoid leukaemia (ALL) in light of potential candidate gene-environment interactions.

Methods: Analyses were based on a subset of 434 cases of ALL and 442 controls successfully genotyped and of European ancestry children enrolled in a French population-based case-control study conducted in 2003–2004. Information about medical history was obtained during a standardized interview with the mothers. Candidate polymorphisms in genes of the Th2 cytokines IL4, IL10, IL13 and IL4-receptor, were genotyped or imputed.

Results: None of the variant alleles were directly associated with childhood acute lymphoid leukaemia. A medical history of asthma or eczema was reported more often in the control group (OR = 0.7 [0.5–1.0]). This association was mostly seen in the group of children not carrying the *IL13*-rs20541 variant allele (Interaction Odds Ratio IOR 1.9, p-interaction = 0.07) and in those carrying the *IL10* triple variant haplotype (IOR 0.5, p-interaction = 0.04). No interaction was observed with the candidate polymorphisms in *IL4* and *IL4R*.

Conclusion: This study provides a new insight into the relationship between allergic symptoms and childhood acute lymphoid leukaemia, by suggesting this inverse association could be limited to children carrying certain genetic polymorphisms. If confirmed, these results could help better understand the biological mechanisms involved in the development of childhood acute lymphoid leukaemia.

Abreviations: ALL, acute lymphoid leukaemia; OR, odds ratio; SNPs, single nucleotide polymorphisms; IL, interleukins

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1. Introduction

Acute lymphoid leukaemia (ALL) accounts for approximately 80% of all childhood acute leukaemias and a quarter of all childhood neoplasms in developed countries. Little risk factors have been identified to date, i.e. high-level ionizing radiation, certain chemotherapeutic agents, Down's syndrome and a few rare genetic disorders. It has long been hypothesized that a lack of immune stimulation through exposure to infectious agents in infancy and early childhood could be related to the development of ALL [1], although the epidemiological evidence is still contradictory [2]. To some extent, this parallels the hygiene hypothesis, which postulates that a lack of early immune stimulation could be associated with the rising incidence of allergies in developed countries. From these, one could expect atopy and allergy to be positively associated with childhood leukaemia. However, most questionnaire-based epidemiological studies reported an inverse association between atopy or allergy and childhood leukaemia, as reviewed by Linabery [3,4].

In the last few years, in an attempt to rely on unbiased sources of information, several publications have studied the association between atopy or allergy and childhood leukemia relying on objective sources of information, such as medical records [5,6], health claim data [7], and IgE levels at recruitment [8]. Some of those studies [5,8] corroborated the inverse association between allergy and childhood leukaemia found in the interview-based studies, whereas two other studies did not find this association [6,7]. Recently, a Mexican study reported a positive association borderline of significance between bronchial asthma and ALL in children with Down syndrome [9].

Despite the increasing biological knowledge, the mechanisms leading to allergy still need to be unraveled. A role of Th2 cytokines has long been suspected in the etiology of allergy, supported by the key regulatory effects of the interleukins produced by T-lymphocytes undergoing a Th2 differentiation, such as interleukins (IL) IL4, IL10 and IL13. Additionally, some studies have reported associations between asthma and polymorphisms in the genes coding for IL13, IL4, IL10 and IL4R [10–13]. Polymorphisms in *IL13* and *IL4R* were also associated with allergic rhinitis, wheeze, atopic dermatitis in an international study [14].

The role of interleukins in childhood leukaemia has been little investigated. In a Californian study, the levels of IL10 at birth were significantly lower in ALL cases than in controls [15]. In the same study, a genomic analysis showed a slight association between ALL and *IL10* tag-SNPs (Single Nucleotide Polymorphisms) [16]. Recently, two polymorphisms in *IL10* were reported to be associated with childhood leukaemia in Taiwan [17].

The aim of the present study was to provide a new insight in the relationship between allergic disorders and childhood ALL by taking into account genetic polymorphisms of several Th2 cytokines, namely interleukins IL4, IL10, IL13 and IL4-receptor, suspected to be involved in the development of allergy.

2. Material and methods

2.1. Study

Study design and sampling have been extensively described elsewhere [18,19]. Briefly, the ESCALE study is a population-based case-control study conducted in France in 2003–2004. Eligible children were residing in mainland France, had not been adopted, and had a living French-speaker biological mother without a serious psychiatric disorder.

Children diagnosed with leukaemia before the age of 15, between 01/01/2003 and 31/12/2004, were detected and recruited using the detection system of the French national childhood haematological malignancies registry. Children who were deceased or under palliative care were ineligible. Out of the 714 eligible children diagnosed with acute lymphoid leukaemia, 648 were enrolled in the study (participation rate 91%).

Controls were randomly selected from the general population using random digit dialing contemporaneously with the recruitment of the cases. Quotas were applied to obtain a control group comparable to the whole case group (leukaemias, lymphomas, CNS tumours and neuroblastomas) in terms of gender and age (0–1, 2, 3, 4, 5–6, 7–8, 9–11, 12–14 years) and to the general population regarding the number of children living in the household. The participation rate of the controls was 71%, so that 1681 controls were enrolled out of the 2361 eligible children.

2.2. Information on medical history

Information about socio-demographic characteristics and suspected risk factors, such as maternal exposures during pregnancy, perinatal characteristics, personal and familial medical history was obtained over the telephone. The children biological mothers were interviewed using a standardized questionnaire identical for cases and controls. Before the interview, mothers were asked to have a copy of the child health record on hand, so they could get back to the records if needed. A large proportion of mothers followed this recommendation (97.2% for ALL cases and 98.2% for controls). Mothers were specifically asked whether the participating child had developed asthma or eczema, and, if so, the age at onset. Moreover, a specific item regarded regular intakes of bronchodilators, corticoids, or antihistamines/anti-allergic drugs.

Reported medical history of asthma and eczema were analysed as independent variables. More specific variables were also analysed, considering a latency period of one year by ignoring the asthma or eczema diagnoses that occurred in the year prior to the age at diagnosis (for cases) or recruitment (for controls). For asthma, we also considered the reported treatments with antihistamines, corticoids or bronchodilators.

2.3. Biological specimens

Biological specimens were requested from each participant. They consisted in blood samples taken from cases during care, prior to initiation of chemotherapy, and saliva taken at home using swab brushes for the controls. Biological samples were obtained from 619 ALL cases (96%) and 810 controls (48%).

After DNA extraction, a sufficient DNA quantity was available for genotyping of 513 ALL cases and 570 controls. Cases were genotyped on an Illumina 370k Quad platform (283,027 single nucleotide polymorphisms [SNPs]), and a custom iSelect platform (4868 SNPs) was used for the controls. The comparability of the two genotyping methods was assessed and confirmed by re-genotyping 96 randomly-selected cases on the platform used for the controls (100% agreement). Fulfilled quality checks, including a call-rate > 97% for the cases and 95% for the controls, and a 46, XX or 46, XY formula were considered mandatory criteria for subsequent genetic analyses, leading to the exclusion of 42 ALL cases (including 6 children with Down syndrome) and 109 controls.

A principal component analysis (PCA) using information from 96,609 SNPs was performed in the case group in order to determine the Caucasian origin from the CEPH (Human Polymorphism Study Center). Because of the platform used for genotyping the controls, such a PCA could not be performed for the control group. However, in the case group, having at least two European-born grandparents, a proxy variable derived from the questionnaire, showed to be very predictive of the CEPH classification (sensitivity 98.2%, specificity 94.3%) [20]. Assuming that this proxy variable was as good a predictor in the control group, it was used to restrict both the case and control samples on European ancestry, in order to limit the potential for population stratification bias.

Finally, 434 cases with ALL and 442 controls, all genotyped children